LOCAL VERSUS SYSTEMIC ANTIHISTAMINES IN TREATMENT OF ALLERGIC RHINITIS

META –ANALYTIC STUDY (A SYSTEMATIC REVIEW)
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Introduction

Allergic rhinitis involves an inflammatory condition affecting the nasal mucosa that may be caused by a variety of different pathologic processes. It may present in affected people with a variety of different symptom patterns, ranging from mildly bothersome and inconsequential to severe and disabling. The presence of rhinitis usually is diagnosed on the basis of the patient's history, supplemented by an examination of the nasal mucous membranes and neighboring structures (Weeke, 1987).

Allergic rhinitis is a common condition in adults and children and can have a large impact on patients' health and quality of life (Baena-Cagnani, 2004).

Approximately 25% of children and 40% of adults in USA are affected by allergic rhinitis during one or more seasons of the year (Smolensky et al, 2007).The prevalence of allergic rhinitis in children has risen significantly over the last two decades (Schenkel, 2000).

As regard pathogenicity of allergic rhinitis we can say that IgE is a homocytotropic antibody which binds to the surface of the mast cell antigen with affinity for IgE triggers conformational change at the cell surface resulting in the release of chemical mediators from the mast cell granules. The mediators: histamine, slow reacting substance of anaphylaxis and eosinophil chemotactic factor cause smooth muscle contraction, increased capillary permeability, eosinophil attraction and increased glandular secretions. The release of mediators from the mast cell granules is controlled by intracellular levels of cyclic nucleotides, particularly, elevated cyclic AMP which inhibits mediator release. Also adrenergic, cholinergic and prostaglandin receptors all influence mediator release (Cooper,1979).

Current treatments for allergic rhinitis include allergen avoidance, systemic antihistamines, and steroidal and non-steroidal intranasal sprays (Shah et al, 2009).

In patients with seasonal allergic rhinitis, intranasal glucocorticoids are more effective than an antileukotriene drug or combined antileukotriene-antihistamine for the reduction of pollen-induced nasal eosinophilic inflammation and for control of nasal symptoms (Pullerits et al, 2002). Although antihistamines and corticosteroids might appear to have complementary mechanisms of action, clinical trials suggest that their co-administration does not confer any additional long-term benefits compared with that achieved with corticosteroids alone (Howarth, 2000).

The available treatment options for pediatric allergic rhinitis, the newer oral antihistamines and intranasal corticosteroids are first-line treatments (Baena-Cagnani, 2004).

Three receptors exist for histamine. H1 receptors are found on blood vessels, sensory nerves, smooth muscles of the respiratory and digestive tracts, and in the central nervous system, their stimulation leads to vasodilatation, increased vascular permeability, sneezing, pruritus, glandular secretion, and increased intestinal motility. H2 receptors have a distribution similar to that of H1 receptors but are principally involved in the regulation of gastric acid secretion. H3 receptors are located principally in the brain and seem to be involved in the regulation of histamine synthesis and release. The contribution of histamine to the early allergic response, largely mediated by the H1 receptor, has long been recognized and is the rationale for the large number of H1 antagonists in clinical use.

Treatment with some antihistamines also reduces the production of leukotrienes and kinins, which are mediators with pro-inflammatory effects, as well as the allergen induced increased responsiveness to methacholine. Another anti-inflammatory property of antihistamines is a reduction of soluble ICAM-1 levels in nasal secretions, a property demonstrated by both loratadine and cetirizine.

Oral antihistamines are readily absorbed. Their onset of action is rapid, usually within 60 minutes, and maximum benefit occurs within hours. Metabolism of most antihistamines occurs primarily through the hepatic cytochrome P-450 system. Drugs that interfere with this system, such as antifungal agents, can lead to the accumulation of antihistamines to toxic levels. One exception is cetirizine, which is primarily excreted in the urine and does not depend on the cytochrome P-450 system. The clinical effectiveness of antihistamines exceeds the duration of measurable serum levels. This phenomenon may be attributable to the presence of active metabolites. Another explanation for the prolonged efficacy of H1 receptor antagonists beyond their measurable serum levels relates to extended tissue levels (Jayant - Robert 2003).

Second-generation antihistamines differ from first-generation ones because of their elevated specificity and affinity for peripheral H1 receptors and because of their lower penetration of the central nervous system (CNS), having fewer sedative effects as a result (Camelo-Nunes, 2006).

The antihistamines, and fundamentally the second generation drugs, have been shown to exert an anti-inflammatory effect, which is greater when the drug is administered continuously than when administered upon demand (Montoro et al, 2007).

Desired properties of antihistamines are rapid onset of action, long duration of efficacy, broad age range of applicability, and potential to improve quality of life (Meltzer,2005).

Cetirizine, the major metabolite of hydroxyzine, is 1 of only 2 oral second-generation antihistamines that have been approved by the Food and Drug Administration for treating children younger than 5 years and 1 of 3 approved for children between 5 and 12 years of age (Galant et al, 2001).

The incidence of sedation associated with cetirizine at the recommended adult dose of 10 mg is less than that seen with first-generation antihistamines but greater than that seen with placebo (Dykewicz et al, 1998).

Similarly, although loratadine has no observable side effects at the standard dose of 10 mg, higher dose can cause performance impairment in some tasks, which has led to concerns about its use in aerospace environment (Hansen, 1999).

In contrast, fexofenadine has been shown to be truly non-sedating and non impairing even at supra clinical doses (Hindmarch et al, 1999).

The intranasal route of administration delivers drug directly to the target organ, thereby minimizing the potential for the systemic adverse effects that may be evident with oral therapy. Furthermore, the topical route of delivery enables the use of lower doses of medication (Salib et al, 2003). Intranasal therapy, which represents a major mode of drug delivery in allergic rhinitis, thus has a very favorable benefit/risk ratio and is the preferred route of administration for corticosteroids in the treatment of this disease, as well as an important option for antihistaminic therapy, particularly if rapid symptom relief is required (Salib et al, 2003).

Levocabastine nasal spray appears to be effective and well-tolerated for the treatment of seasonal allergic rhinitis and is an alternative to oral antihistamines (Dahl et al, 1995). Topical application of levocabastine, a potent H1 antagonist, yielded good clinical results in allergic conjunctivitis, seasonal allergic rhinoconjunctivitis, and non allergic perennial rhinitis (Van de Heyning et al, 1991). Azelastine nasal spray is suitable in the treatment of allergic rhinitis in juvenile patients (Wober et al, 1997).

AIM OF THE WORK

To review systematically the published literature to find out which is better for treating allergic rhinitis: local or systemic antihistamines.

This study was done through the following steps:

1. Determination of the target disease.
2. Identification and location of articles.
3. Screening and evaluation of articles.
4. Data collection.
5. Data analysis.
6. Reporting and interpretation (Results).
7. Discussion and conclusions.

Methodology

1) Determination of target disease:

Which type of antihistamines, local or systemic, is better for treating allergic rhinitis regarding:

1-Functional outcome (decrease of repeated attacks of the disease and the personal sufferings during the day and the night, based on scoring systems e.g. simple scoring system "Ng et al, 2000", Total 4-Symptom Score (T4SS) scoring system for allergic rhinitis symptom score (Yuksel et al, 2009) and total and major symptom complex (TSC, MSC) scores based on 14 symptoms evaluated at 30-minute intervals served as primary efficacy variables (Day et al, 2001)

2-Complications.

2) Identification and location of articles:

Studies included published medical articles concerning the use of local and systemic antihistamines in allergic rhinitis through searching of the Medline database available at (www.pubmed.com) using the keywords: local antihistamines, systemic antihistamines and local and systemic antihistamines AND allergic rhinitis with each of the preceding keywords.

The search was limited to articles published from 1949 up to 31-1-2010 in English language, conducted on humans and yielded 64, 91 and 19 articles respectively.

3) The screening and evaluation:

Articles included were screened to report on at least:

1- Comparison between local and systemic antihistamines in efficacy on the long run.

2- Comparison between local and systemic antihistamines, as regard safety and side effects on the long run.

The screening criteria were used by investigators to screen the articles yielded by the Medline search after blinding the articles regarding authors and journal of publication. Only articles fulfilling the criteria of screening (minimal required data as seen by screening will be the 2 items mentioned above) were included for further steps of data collection, analysis and reporting.

4) Data collection:

In each included study we:

1-determined the sample size.

2-determined number of patients in study and control group.

3-explained the pre-treatment status of the study and control groups.

4-illustrated the details of interventions.

5-mentioned the outcome measures.

For each article the following were recorded in the software used in the steps of data analysis, interpretation and reporting:

1 Type of the study.
2 Number of cases reported in the article.
3 Outcomes, complications and follow up period.